REMARKS

Provisional Double Patenting Rejection of Claims 10, 11 and 18

Claims 10, 11 and 18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claim 1 of copending Application No. 10/686,943 . . . for reasons of record" (Office Action, page 3). As acknowledged by the Examiner in the instant Office Action (page 3), Applicants will address the provisional double patenting rejection once an indication of allowable subject matter has been made.

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al. (WO 98/56919) and Kazanji et al. (International Journal of Cancer, 1997, Vol. 71, pages 300-307 – IDS filed on 3-21-2002)" (Office Action, page 4). The Examiner states that "[c]ontrary to Applicant's assertion, Kazanji et al. explicitly disclose that WKY rats were primed with DNA plasmids containing HTLV-1-*env gp46* gene and boosted with Ad5 containing the HTLV-1-*env gp46* gene (see abstract, bridging paragraph of columns 1 and 2 on page 303 and column 2 of page 304)" (Office Action, page 5). The Examiner also states that "Kazanji et al. disclose that WKY rats primed with pMLP-KTLV-I-*env* and posted [sic] with Ad5-HTLV-I-*gp46* induced a CTL response against HTLV-I transformed cells (see page 304, column 2)" (Office Action, page 6). The Examiner concludes that "it would have been obvious for one of ordinary skill in the art at the time the invention was made to use the adenovirus vectors disclosed by Kazanji et al. in the compositions and methods disclosed by McMichael et al. in order to take advantage of the ability of the adenovirus vectors to be orally administered and to be cheaply made" (Office Action, page 7).

Applicants respectfully disagree. The combined teachings of the cited references, as a whole, do not suggest that substituting the non-replicating or replication-impaired recombinant poxvirus vector in the heterologous prime-boost method of McMichael *et al.* with any of the vectors mentioned by Kazanji *et al.* would yield a predictable or successful induction of a CD8+ T cell immune response to an antigen in an individual.

The present rejection appears to be based on an incorrect interpretation of certain sentences in the Kazanji *et al.* reference. In particular, the Examiner appears to rely on the following statements to support the conclusion that "Kazanji *et al.* disclose the administration of naked DNA plasmids containing the HTLV-I-*env* gene as the 'primer' and the administration of Ad5 containing the HTLV-I-*env gp46* gene as the 'booster'" (Office Action, page 7):

> Two immunization regimens against HTLV-I were tested in WKY and Fischer F-344 rats. The first involved WKY rats primed with Ad5-HTLV-I-env ***or*** naked DNA plasmids containing the HTLV-I-env gene ***and*** boosted with Ad5 containing the HTLV-I-env gp46 gene ***or*** with baculovirus-derived recombinant gp46. (Abstract, emphasis added);
>
> The results presented in Figure 4 show that CTL were detected to the same extent in rats immunized with either Ad5-HTLV-1-env ***or*** pMLP-HTLV-I-env, ***and*** that the nature of the boosting with gp46 ***or*** Ad5-HTLV-I-gp46 ***or*** pMLP-HTLV-I-gp46 did not change the level of the response. (Paragraph bridging columns 1 and 2 on page 303, emphasis added);
>
> and
>
> The WKY rats primed with Ad5-HTLV-I-env ***or*** pMLP-HTLV-I-env, ***and*** boosted with gp 46 ***or*** Ad5-HTLV-I-gp46 ***or*** pMLP-HTLV-I-gp46, failed to produce antibodies against HTLV-I enevelop protein. . . However, the immunized and boosted WKY rats developed a CTL response against syngeneic HTLV-I-transformed cells. (page 304, column 2, emphasis added).

The three passages listed above refer to priming with an adenovirus "or" DNA plasmid "and" boosting with an adenoviral vector, a recombinant protein "or" a DNA plasmid. It appears that the Examiner has interpreted the use of the word "or" in these sentences to mean that all possible combinations of the priming and boosting vectors mentioned were tested in the disclosed experiments, including:

- homologous Ad5-HTLV-1-*env* prime/Ad5-HTLV-1-*gp46* boost;
- homologous pMLP-HTLV-I-*env* prime /pMLP-HTLV-I-*gp46* boost;
- heterologous Ad5-HTLV-1-*env* prime/pMLP-HTLV-I-*gp46* boost;
- heterologous pMLP-HTLV-I-*env* prime/Ad5-HTLV-1-*gp46* boost;
- heterologous Ad5-HTLV-1-*env* prime/recombinant *gp46* boost; and
- heterologous pMLP-HTLV-I-*env* prime/ recombinant *gp46* boost.

When read in isolation, the sentences quoted above are ambiguous as to whether some or all of these combinations were tested. However, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). A close reading of the Kazanji *et al.* reference as a whole reveals that Kazanji *et al.* did not perform a heterologous prime-boost regimen using a DNA plasmid prime and an adenovirus vector boost, nor do they teach or suggest such a regimen. For example, the paragraph that bridges columns 1 and 2 on page 303, which was cited by the Examiner in the Office Action to support the conclusion that Kazanji *et al.* disclose priming with a DNA plasmid and boosting with an adenovirus vector, refers directly to results presented in Figure 4. Figures 4A-D on page 305 of Kazanji *et al.* depict the amounts of cytotoxic activity in spleen-cell cultures of rats that were immunized with the various combinations of vectors listed in the upper left corner of each respective graph. Significantly, the combination of a DNA plasmid (pMLP-HTLV-I-env) prime and adenovirus (Ad5-HTLV-1-gp46) boost is not listed among the sixteen experimental groups shown in Figures 4A-D or their corresponding figure legend. Clearly, the paragraph that bridges columns 1 and 2 on page 303 does not relate to an experiment that involved a DNA plasmid prime and an adenovirus vector boost.

Additional support for the conclusion that Kazanji *et al.* did not perform a heterologous prime-boost regimen using a DNA plasmid prime and an adenovirus vector boost can be found in the Materials and Methods section, as well as Table I, of the reference. Specifically, at the bottom of column 1 on page 301, in the section entitled "*Animals, vaccination regimens and challenge with HTLV-I*," Kazanji *et al.* state that that "[t]he vaccination protocols using different vectors are shown in Table I (A, B and C)." Only Table IA relates to vaccination protocols that employed an adenovirus vector (Ad5-HTLV-I). Table IA clearly shows that a homologous Ad5-HTLV-I-*env* prime/Ad5-HTLV-I-*gp46* boost regimen and a heterologous Ad5-HTLV-I-*env* prime/ recombinant gp46 protein (Baculo.rgp46) boost regimen were performed. However, neither Table IA, B nor C indicates that a heterologous prime-boost regimen using a DNA plasmid prime and an adenovirus vector boost was carried out. If such a heterologous prime-boost regimen had been performed, it is expected that Kazanji *et al.* would have indicated this in

Table IA, B or C, or in one of the figures that describes the results of their immunization experiments.

In view of the above remarks, and in light of the entire disclosure in Kazanji *et al.*, Applicants respectfully request that the Examiner reconsider his position as to whether Kazanji *et al.* actually disclose priming of WKY rats with DNA plasmids containing HTLV-1-env gp46 gene and boosting with Ad5 containing the HTLV-1-env gp46 gene.

Although, as the Examiner points out, the instant claims are not directed to methods of inducing a protective immune response (Office Action, page 5), one of skill in the art would clearly seek to induce a CD8+ T cell immune response to generate protection against a virus. As discussed in the Reply filed on September 4, 2007, Kazanji *et al.* teach that only WKY-vaccinated rats that were subjected to a homologous prime-boost vaccination protocol were protected from subsequent HTLV-1 infection (see Kazanji *et al.*, page 303, column 2, last paragraph and Table II), thereby discouraging one of skill in the art from using a heterologous prime-boost regimen.

McMichael *et al.* disclose heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen. In addition, McMichael *et al.* disclose boosting compositions for their heterologous prime-boost methods that comprise a non-replicating or replication-impaired recombinant poxvirus vector. However, McMichael *et al.* do not disclose non-replicating or replication impaired adenovirus vectors.

The combined teachings of Kazanji *et al.* and McMichael *et al.* do not teach or suggest that one of skill in the art should substitute the non-replicating or replication-impaired recombinant poxvirus vector in the boosting composition of McMichael *et al.* with the adenoviral vector of Kazanji *et al.* to practice Applicants' claimed heterologous prime-boost method of inducing a CD8+ T cell immune response to an antigen in an individual. There is no teaching or suggestion in the McMichael *et al.* reference or the Kazanji *et al.* reference as a whole to suggest the desirability, and thus obviousness, of using the adenovirus vector of Kazanji *et al.* in the heterologous prime boost method of McMichael *et al.*

Thus, Applicants' claimed methods are not rendered obvious by the combined teachings of McMichael *et al.* and Kazanji *et al.*

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al. (WO 98/56919) and Natuk et al., 1993, AIDS Research and Human Retroviruses, Vol. 9 No 5, pages 395-404 – IDS filed on 3-21-2002) . . . for reasons of record" (Office Action, page 7). According to the Examiner, "Natuk et al. disclose not only the efficacy of replication deficient adenovirus vectors but also disclose the drawbacks of using replication competent adenoviruses (*i.e.* the induction of neutralizing antibodies etc.) [see page 402]" (Office Action, page 8). The Examiner states that, "in view of the KSR decision, since the use of replication-deficient adenovirus vectors is well known in the art yielding predictable results, it is obvious for the skilled artisan to use them in the methods of McMichael et al." (Office Action, page 8).

Applicants respectfully disagree. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). The combined teachings of the cited references, as a whole, do not suggest that substituting the non-replicating or replication-impaired recombinant poxvirus vector in the method of McMichael *et al.* with the replication-defective adenovirus mutant vector mentioned by Natuk *et al.* would yield a predictable or successful induction of a CD8+ T cell immune response to an antigen in an individual.

Natuk *et al.* teach that a "key issue regarding the utility of adenovirus vectors as vaccines is whether recombinant adenovirus replication will occur in individuals that possess preexisting immunity to the vector and whether the amount of recombinant antigen expression resulting from such infections is sufficient to stimulate strong immune responses to the foreign antigen" (Natuk *et al.*, page 402, left column; emphasis added).

Natuk *et al.* do not teach that the induction of neutralizing antibodies to adenovirus is a drawback of using replication competent adenoviruses, as suggested by the Examiner (Office Action, page 8). Rather, in paragraph 2 on page 402, Natuk *et al.* advocate using replicating adenoviruses to overcome the problems associated with preexisting serum antibodies to adenovirus (see page 402, paragraph 2). Specifically, Natuk *et al.* teach that intranasal immunization "would be a particularly attractive immunization route to pursue if virus

replication is consistently established in individuals possessing preexisting serum antibody to adenovirus" (see page 402, column 2, second sentence of second paragraph, emphasis added).

Furthermore, in paragraph 3 on page 402, Natuk *et al.* teach that intranasal inoculation of Ad7-HIV into chimpanzees that had moderate or no anti-Ad7 neutralizing antibodies did not induce overt signs of clinical illness (see page 402, third paragraph of column 2). These results attest to the potential safety of the replication-competent Ad7 vector and do not teach or suggest that neutralizing antibodies are induced by, or are a drawback of, immunization with replicating adenovirus.

To support the conclusion that Natuk *et al.* disclose "the efficacy of replication deficient adenovirus vectors," the Examiner refers to page 402 of Natuk *et al.*, where the authors mention that intranasal immunization with replication-defective adenovirus mutants could be pursued as a possible alternative to intranasal immunization with replicating adenoviruses that are not fully attenuated (see page 402, column 2, last sentence of second paragraph). However, as discussed above, Natuk *et al.* explicitly teach in the same paragraph that intranasal immunization "would be a particularly attractive immunization route to pursue if virus replication is consistently established in individuals possessing preexisting serum antibody to adenovirus" (see page 402, column 2, second sentence of second paragraph, emphasis added). Thus, Natuk *et al.* suggest that adenovirus replication is important for efficacy in individuals who possess serum antibodies against adenovirus, and direct one of skill in the art to use a replicating adenovirus for intranasal immunization. Moreover, as noted by Natuk *et al.*, preexisting serum antibody to adenovirus was recognized at the time of the invention to be a significant obstacle to the use of adenoviral vectors for therapeutic purposes. Accordingly, one of skill in the art would have been concerned about overcoming preexisting serum antibody to adenovirus and, therefore, would have been motivated by the teachings in Natuk *et al.* to use an adenovirus that is attenuated in ways that do not affect its replication.

The mere mention of possible alternatives to replicating adenoviruses, such as adenovirus with temperature-sensitive lesions or replication-defective adenovirus mutants, does not constitute a teaching that such alternatives are efficacious or likely to yield a predictable result. Clearly, the teachings on page 402 of Natuk *et al.* do not provide a reasonable expectation of success in using replication-defective adenovirus mutants to induce a CD8+ T cell immune

response to an antigen in a subject, especially in subjects possessing preexisting serum antibodies to adenovirus.

Thus, in considering the teachings of Natuk *et al.* as a whole, including the teachings on page 402, it is clear that Natuk *et al.* direct one of skill in the art to use replicating adenovirus vectors in HIV vaccines.

Combination of Natuk et al. and McMichael et al.

In the instant Office Action, the Examiner states that, "in view of the KSR decision, since the use of replication-deficient adenovirus vectors is well known in the art yielding predictable results, it is obvious for the skilled artisan to use them in the methods of McMichael et al." (Office Action, page 8).

Applicants respectfully disagree that the use of replication-deficient adenovirus vectors was well known in the art yielding predictable results at the time of the invention. For example, McMichael *et al.* disclose heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen comprising administering a boosting composition comprising a non-replicating or replication-impaired recombinant poxvirus vector that is a source of one or more CD8+ T cell epitopes of the target antigen (McMichael *et al.*, page 10, lines 6-24). McMichael *et al.* teach that

> It has now been discovered that non-replicating and replication-impaired strains of poxvirus provide vectors which give extremely good boosting effect to a primed CTL response. Remarkably, this effect is significantly stronger than a boosting effect by wild type poxviruses.

(McMichael *et al.*, page 8, lines 13-17, emphasis added).

Thus, McMichael *et al.* teach that the efficacy of non-replicating or replication-impaired recombinant poxvirus vectors as boosting compositions in heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen was surprising and, thus, could not be predicted based on the teachings of the prior art. Moreover, McMichael *et al.* fail to provide a teaching or suggestion that the unexpected results of their methods could be achieved using any non-replicating or replication-impaired viral vector other than a non-replicating or replication-impaired recombinant poxvirus as a boosting vector. In fact, McMichael *et al.* demonstrate that priming with plasmid DNA and boosting with recombinant MVA was more immunogenic than

the reverse order of immunization (MVA/DNA) (McMichael *et al.*, page 30, lines 24-26). Replacing the MVA vector of McMichael *et al.* with the adenoviral vector of Natuk *et al.* is an even more drastic alteration of the method of McMichael *et al.* than reversing the order of the priming and boosting vectors. Therefore, one of skill in the art would not reasonably expect that such a significant alteration in the method of McMichael *et al.* would induce a successful CD8+ T cell immune response against a target antigen.

Clearly, the teachings of McMichael *et al.* as a whole suggest that the specific use of a boosting composition comprising a non-replicating or replication-impaired recombinant poxvirus vector is a critical component of their surprising heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen. Accordingly, McMichael *et al.* direct one of skill in the art to use a non-replicating or replication-impaired recombinant poxvirus vector in their heterologous prime-boost methods.

Natuk *et al.* do not teach or even suggest that the use of a replication-deficient adenoviral vector would yield a predictable induction of a CD8+ T cell immune response to an antigen in a subject.

The combined teachings of McMichael *et al.* and Natuk *et al.* do not teach or suggest that the induction of a CD8+ T cell immune response to an antigen in a subject is predictable when a replication-deficient adenoviral vector is employed in the heterologous prime-boost method of McMichael *et al.*, nor do the combined teachings of the cited references provide a reasonable expectation of success in inducing a CD8+ T cell immune response to an antigen in a subject by practicing the heterologous prime-boost method of McMichael *et al.* using a replication-deficient adenoviral vector in place of a non-replicating or replication-impaired recombinant poxvirus vector.

Thus, the combined teachings of McMichael *et al.* and Natuk *et al.* do not render Applicants' claimed invention obvious.

Sixth Supplemental Information Disclosure Statement

A Sixth Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested. Copies of the cited references, C13-C15 and C26-C28, were submitted with Information Disclosure Statements

(IDSs) that were previously filed, and fully considered and acknowledged, in this application (see IDS filed on July 31, 2006 and Office Action dated May 30, 2007). In order to comply fully with 37 C.F.R. §§ 1.97 and 1.98, citations for these references on the attached Listing of References have been revised to include dates, which were lacking in the IDS filed on July 31, 2006.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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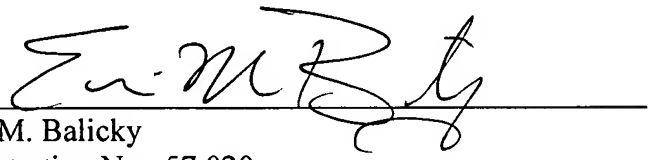
By 

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